Predicting Ventilation Failure in Children With Inhalation Injury

By John C. Fitzpatrick, William G. Cioffi, Jr, Henry W. Cheu, and Basil A. Pruitt, Jr
San Antonio, Texas

● **Despite advances in mechanical ventilatory support for patients with smoke inhalation injury, including the use of high-frequency flow-interruption ventilators such as the VDR, inhalation injury alone may increase mortality by as much as 20% in patients with thermal injury, and up to 60% when pneumonia occurs. Inhalation injury causes a primary large and small airway epithelial insult that results in ventilation abnormalities, rather than a primary alveolar lesion that results in oxygenation abnormalities as occur in multiple-system organ failure. Patients with inhalation injury requiring high ventilatory pressures experience complications of barotrauma and frequently succumb to necrotizing tracheobronchitis and oxygenation abnormalities after 2 to 4 weeks of mechanical ventilation. Ventilatory indexes obtained early in the postburn period allow the development of accurate predictive formulae that identify patients who will not be adequately supported by mechanical ventilation after smoke inhalation injury. Early identification of such patients will allow rapid conversion to other methods of ventilatory support that effect gas exchange, with minimal risk of further barotrauma, while inhalation injury healing occurs. Such predictors may be developed for other disease processes that are characterized by severe pulmonary ventilatory dysfunction.**

INDEX WORDS: Ventilation failure predictor, inhalation injury, children.

INHALATION injury, which occurs in up to 30% of thermally injured patients,[1] increases age- and burn size-related mortality by a maximum of 20% alone, and up to 60% when pneumonia occurs.[2,3] Conventional treatment involves the use of supplemental oxygen, assiduous pulmonary toilet, and volume-controlled positive pressure ventilators for patients requiring mechanical ventilatory support. Recent clinical trials employing pressure-controlled high-frequency flow-interruption ventilation have demonstrated its efficacy (decreased mortality) in comparison to conventional ventilation.[1,4,5]

Even with advances in therapy for inhalation injury, the lowest reported mortality rates are still at least 20%. Barotrauma resulting from mechanical ventilation compounds the initial injury.[6,7] Prospective early identification of patients who will not be supported adequately by mechanical ventilation would allow rapid enrollment of these patients in trials of new support techniques such as extracorporeal CO_2 removal, intravenous oxygenation, intratracheal pulmonary ventilation, combined liquid-gas ventilation, or extracorporeal membrane oxygenation (ECMO), to minimize additional injury from barotrauma. This study retrospectively assesses differences in ventilatory, burn, and demographic indexes among 10 survivors and four nonsurvivors with severe inhalation injury to generate predictive equations for outcome by postburn day 2, using stepwise discriminant function analysis.

MATERIALS AND METHODS

Fourteen patients ≤18 years of age with severe smoke inhalation injury (diagnosed by bronchoscopy) requiring intubation and mechanical ventilation admitted on postburn days 0 to 2 from May 1989 to March 1993 were studied. Standard bronchoscopic criteria were used to make the diagnosis of inhalation injury.[8] The criteria include diffuse patchy epithelial erythema, the presence of carbonaceous material distal to the vocal cords, epithelial ulcerations, sloughed tracheal mucosa, and hemorrhagic casts consisting of blood and necrotic debris. The records of all patients were reviewed for age, gender, outcome, percentage of total body surface burned, percentage of third-degree burn, and ventilatory indexes (at 6 AM daily) on postburn days 0 to 2 (peak inspiratory pressure, ventilator rate, and positive end-expiratory pressure). The rate-pressure product (RPPROD) was calculated by multiplying peak inspiratory pressure by ventilator rate. Thirty-two sets of data were obtained from the records—24 for the 10 survivors, and eight for the four nonsurvivors.

Ventilator management for patients with inhalation injury at our institution include the use of high-frequency flow-interruption ventilation, permissive hypercapnia to decrease the risk of barotrauma, and maintenance of oxygen saturation greater than 93%. Arterial pH above 7.32 is considered acceptable; peak inspiratory pressures producing arterial P_{CO_2} of less than 30 mm Hg are not used to compensate for metabolic acidosis. Positive end-expiratory pressures, high-frequency rate, inspiratory:expiratory (I:E) ratio, and F_{IO_2} sufficient to attain appropriate oxygen saturation and functional residual capacity above closing volume were used. Typical initial ventilator settings include peak inspiratory pressure of 25 cm H_2O, rate of 20 breaths per minute, inspiratory:expiratory time ratio of 1:1, positive end-expiratory pressure of 3 to 5 cm H_2O,

From the US Army Institute of Surgical Research and the Wilford Hall Air Force Medical Center, San Antonio, TX.

Presented at the 1993 Annual Meeting of the Section on Surgery of the American Academy of Pediatrics, Washington, DC, October 29-31, 1993.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Departments of the Army, Air Force, or Defense. Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations. All material in this article is in the public domain.

Address reprint requests to John C. Fitzpatrick, MD, US Army Institute of Surgical Research, SGRD-USC-B, 2322 Harney Rd, Ft Sam Houston, TX 78234-6315.

0022-3468/94/2908-0035$00.00/0

high-frequency rate of 10 Hz (600 cycles per minute), and F_{IO_2} of 1.0, followed by frequent serial adjustments to achieve desired gas exchange with minimal pressures and inspired oxygen concentration.

Statistical Analysis

Data were examined by Fisher's exact test and the unpaired *t* test, as appropriate, to determine significant differences between survivors and nonsurvivors. A *P* value of less than .05 was considered statistically significant. Equations predicting outcome were developed using stepwise discriminant function analysis. The entire data-set and a subset of data consisting of the worst ventilator settings (determined by the highest RPPROD) during postburn days 0 to 2 for each patient were used to generate separate statistics for four variables (peak inspiratory pressure, ventilator rate, positive end-expiratory pressure, and RPPROD) and predictive equations for comparative purposes. Fisher's exact and unpaired *t* test results were calculated using Statview 4.01 (Abacus Concepts, Berkeley, CA). Stepwise discriminant function analyses were calculated using BMDP Statistical Software (Los Angeles, CA), release 7.0 (VAX/VMS).

RESULTS

Peak inspiratory pressure, positive end-expiratory pressure, and RPPROD were significantly different between groups in both data-sets (Table 1). Ventilator rate differences were significant for all observations and nearly significant for the worst observation. Differences in age, gender, total burn size, or third-degree burn size between survivors and nonsurvivors were not significant in this small group of patients (Table 2). Stepwise discriminant function analysis was applied to both data-sets to select independent predictors of outcome. RPPROD was identified as the only independent predictor of outcome in both data-sets (Table 3). The predictive equations for all observations were $y = -1.76 + 0.00395 \times$ RPPROD for survivors and $y = -6.56 + 0.00927 \times$ RPPROD for nonsurvivors. The larger "*y*," calculated by the two equations, predicts group membership. These equations also may be solved to identify the RPPROD yielding an even chance of group assignment. For this data-set, this occurs at RPPROD = 902. RPPRODs of less than 902 predict survival; values above 902 predict nonsurvival. Using these equations, 95.8% (23/24, sensitivity) of the RPPRODs accurately reflected survival, and 62.5% (5/8, specificity) accurately reflected nonsurvival. The positive predictive value of the equations (true-positive/true-positive + false-positive) is 88.5%; the negative predictive value (true-negative/true-negative + false-negative) is 83.3%. The expected accuracy of any prediction (true-positive + true-negative/number of patients) is 87.5%. Cross-validation tests (jackknifed classification as well as 80% random subset) produced identical patient identification. The predictive equations for the worst observation data-set were *y* =

Table 1. Summary of Differences Between Survivors and Nonsurvivors (Days 0 to 2)

Variable	Survivors (n = 10)	Nonsurvivors (n = 4)	*P*
Peak inspiratory pressure (cm H_2O)			
All observations	28.0 ± 8.0	44.4 ± 17.4	.0009
Worst observation	28.9 ± 8.2	47.0 ± 20.2	.0292
Ventilatory rate (breaths/min)			
All observations	19.3 ± 5.9	27.6 ± 7.5	.0029
Worst observation	20.5 ± 6.9	29.0 ± 8.8	.0775
Positive end-expiratory pressure (cm H_2O)			
All observations	4.7 ± 1.6	7.8 ± 3.0	.0008
Worst observation	4.7 ± 1.5	7.5 ± 2.9	.0272
Rate-pressure product			
All observations	540 ± 223	1266 ± 649	<.0001
Worst observation	589 ± 259	1375 ± 682	.0069

NOTE. Data are expressed as mean ± SD.

Table 2. Summary of Differences Between Survivors and Nonsurvivors (Days 0 to 2)

Variable	Survivors (n = 10)	Nonsurvivors (n = 4)	*P*
Age (yr)	8.6 ± 5.9	4.3 ± 1.7	0.1844
Total burn surface area (%)	28.2 ± 24.9	49.1 ± 33.5	0.2196
Third-degree burn (%)	15.0 ± 23.2	36.4 ± 37.1	0.2107
Gender (female:male)	3:7	2:2	0.5804

NOTE. Data are expressed as mean ± SD.

Table 3. Stepwise Discriminant Function Analyses

	Alive	Dead	% Correct
All observations, days 0 to 2 (F = 23.139, $P \leq .0001$)			
Survivors (24): $y = -1.76 + 0.00395 \times$ RPPROD	23	1	95.8
Nonsurvivors (8): $y = -6.56 + 0.00927 \times$ RPPROD	3	5	62.5
Sensitivity: 23/24 = 95.8%	Positive predictive value: 23/26 = 88.5%		
Specificity: 5/8 = 62.5%	Negative predictive value: 5/6 = 83.3%		
	Accuracy of any result: 28/32 = 87.5%		
Worst observation, days 0 to 2 (F = 10.591, P = .0069)			
Survivors (10): $y = -1.73 + 0.00353 \times$ RPPROD	9	1	90.0
Nonsurvivors (4): $y = -6.37 + 0.00825 \times$ RPPROD	1	3	75.0
Sensitivity: 9/10 = 90.0%	Positive predictive value: 9/10 = 90.0%		
Specificity: 3/4 = 75.0%	Negative predictive value: 3/4 = 75.0%		
	Accuracy of any result: 12/14 = 85.7%		

Abbreviation: RPPROD, rate-pressure product.

$-1.73 + 0.00353 \times$ RPPROD for survivors and $y = -6.37 + 0.00825 \times$ RPPROD for nonsurvivors. Solving for RPPROD in this data-set yields a value of 983. Using these equations, the sensitivity was 90.0% among survivors, and the specificity was 75.0% among nonsurvivors. The positive predictive value of the equations is 90.0%; the negative predictive value is 75.0%. The expected accuracy of any prediction is 85.7%.

The causes of death for the four nonsurvivors were acute ventilatory failure (2) and multiple-system organ failure with significant pulmonary injury (2). One patient with a preexisting upper respiratory tract infection before sustaining his inhalation injury was placed on ECMO after 8 days of mechanical ventilation on the VDR (Volumetric Diffusive Respirator; Bird Space Technologies, Percussionaire Corp, Sand Point, ID) when it became impossible to ventilate him because of overwhelming pneumonia. The deaths of the three patients maintained on mechanical ventilation were directly attributable to pulmonary dysfunction. The patient placed on ECMO, although a nonsurvivor, had recovered from inhalation injury and pneumonia before death (see below). His death was attributed to complications of ECMO, but ECMO had been used as a salvage therapy because of otherwise lethal pulmonary dysfunction.

For all observations, misclassifications occurred in three patients. The patient who lived but was misclassified as a nonsurvivor was a 15-year-old girl who had difficulty synchronizing with the ventilator on her first postburn day; but with sedation, she was able to be ventilated easily and had an otherwise uncomplicated course. Two patients who died had been misclassified as survivors a total of three times. One patient was a 2-year-old girl who had been properly classified at the time of admission but sustained barotrauma complications (bilateral pneumothoraxes with large air leaks requiring multiple chest tubes) later on postburn day 0. Because of these complications and difficulty in maintaining acceptable ventilatory goals, she was placed on reduced ventilatory support and was given large doses of tris-hydroxymethylaminomethane for control of acidosis; this led to an unrealistically low RPPROD, resulting in misclassification on the morning of her first postburn day. She died later on the first postburn day. The second patient, a 6-year-old boy (described above) was misclassified twice; he had an upper respiratory tract infection at the time of his burn and did not require excessive ventilatory support early in his course, but he did meet nonsurvivor criteria by the morning of his fourth postburn day. Later in his hospital course (postburn day 5) he had overwhelming staphylococcal pneumonia and could not be supported by mechanical ventilation. He was placed on ECMO and died of septic cerebral abscesses and myocardial failure. In the worst-observation data-set, the misclassified patients were the 15-year-old girl and the 6-year-old boy.

DISCUSSION

Inhalation injury causes damage to large and small airways, characterized by tracheobronchial epithelial necrosis and sloughing; disorientation, clumping and loss of cilia; and decreased mucociliary clearance.[9] Edema resulting in narrowing of airway caliber and obstructive debris composed of epithelium and mucus combine to cause airway obstruction. Overdistention and barotrauma occur in some alveoli (by a ball-valve mechanism) and complete obstruction with atelectasis in others. If persistent, these ventilation abnormalities prevent healing of the original inhalation injury and cause damage to previously normal alveoli, eventually leading to ventilatory failure; oxygenation failure may also occur due to increased pulmonary shunt. This is in contradistinction to primary alveolar pathology, which results in severe oxygenation abnormalities such as that seen in cases of adult respiratory distress syndrome (ARDS). Patients with inhalation injury requiring high ventilatory pressures experience complications of barotrauma and frequently succumb to necrotizing tracheobronchitis and oxygenation abnormalities after 2 to 4 weeks of mechanical ventilation.

Mechanical ventilation is itself associated with a number of serious complications that have significant effects on morbidity and mortality. These complications include pneumothorax, pneumomediastinum, subcutaneous emphysema, pneumoperitoneum, bronchopulmonary dysplasia, decreased static lung compliance, necrotizing tracheobronchitis, bronchopneumonia, atelectasis, and decreased surfactant function.[4,6,9,10] Current theories regarding the etiology of these complications incorporate some or all of the following: barotrauma, inadequate humidification, inadequate clearance and subsequent inspissation of secretions, and ventilation at pressures and volumes that do not allow for recruitment of atelectatic or damaged alveoli.[5,6,7,9,11,12] Persistent nonhealing pulmonary injury or exacerbation of the original injury by these iatrogenic complications adversely affect patient outcome. These therapeutic problems have been significantly decreased but not eliminated by the use of high-frequency flow-interruption ventilators like the VDR. It is desirable to determine rapidly which patients will likely fail to be supported adequately by mechanical ventilation; they should be considered for more invasive support, such as ECMO,

or experimental protocols such as extracorporeal CO_2 removal, intravenous oxygenation, intratracheal pulmonary ventilation, total liquid ventilation, or perfluorocarbon-associated gas exchange; these methods allow for relative lung rest while respiratory function is maintained.

The ventilatory management used in the present series was provided by a pressure-controlled high-frequency flow-interruption ventilator.[1,4,5] The patient is ventilated by controlled stacking of subtidal breaths during a preselected inspiratory time to a preselected peak inspiratory pressure, followed by passive exhalation (Fig 1). The high-frequency component entrains a high-flow bypass ventilatory gas mixture. As the patient is ventilated, injured airways and alveoli are opened gently by the repeated small incremental increases in airway pressure during inspiration. Barotrauma to normal alveoli is minimized through improved distribution of ventilatory gases, with resulting decreased peak and mean airway pressures caused by recruitment of damaged alveoli. The VDR is very efficient at improving oxygenation due to maintenance of recruitment. Combined with the relative lack of alveolar pathology, oxygenation is rarely a problem (alveolar-arterial $DO_2 < 250$ for all patients in this study) unless the patient progresses to ARDS. The frequency may be varied from 5 to 15 Hz (300 to 900 cycles per minute) depending on the specific clinical need; oxygenation is improved at higher frequencies, whereas CO_2 clearance is improved at lower frequencies. The high-flow bypass gas necessary for entrainment by the high-frequency component of the ventilator makes measurement of proximal mean airway pressures difficult and precludes meaningful assessment of the oxygenation index. New technology such as catheter tip transducers may make measurement of mean airway pressure and other airway pressures at various times of the ventilatory cycle possible; these techniques are presently being evaluated.

Many different calculated respiratory and ventilatory indexes exist that may be used to identify patients who should be considered for ECMO or the experimental protocols listed above. Routine predictive indexes rely on oxygenation defects such as alveolar-arterial oxygenation gradient greater than 600 mm Hg for longer than 4 hours (Lotze criteria) or longer than 8 hours (Beck criteria),[13] or a combination of oxygenation defects and mean airway pressure (oxygenation index greater than 40 for three of five arterial blood gases obtained 0.5 to 1 hour apart), without addressing fully the issue of barotrauma. Barotrauma is one indication for the use of more invasive ventilatory therapy, but only after it occurs, not by virtue of the potential for iatrogenic injury. In particular, inhalation injury is inherently difficult to assess by these indexes because CO_2 clearance, management of secretions, and control of airway pressures are the major clinical problems in the ventilatory management of these patients. Oxygenation alone is rarely a significant problem early in the course of inhalation injury. The optimal ventilator modality currently available for respiratory management in this disease process (high-frequency flow-interruption) makes reproducible calculation of oxygenation index technically difficult.

These considerations favored the development of a different type of predictor that directly addressed barotrauma. The ideal predictor of outcome should be easily calculated at the bedside and accurately predict ventilatory failure at the earliest possible moment, thus allowing rapid conversion to an alternate form of ventilatory support such as ECMO or inclusion in an experimental ventilatory support protocol designed to minimize the risk of barotrauma. This study demonstrates the utility of RPPRODs for

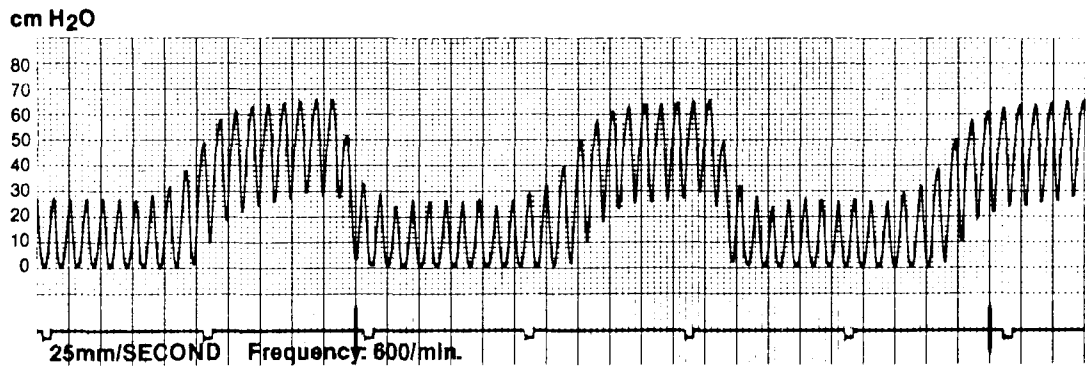

Fig 1. Representative waveform tracing from the proximal airway during ventilation by high-frequency flow interruption (VDR); this demonstrates the controlled stacking of high-frequency subtidal breaths to the preselected peak inspiratory pressure followed by passive exhalation.

predicting failure of mechanical ventilation to adequately support children who have inhalation injury. Recently, others have reported that RPPRODs are useful in predicting outcome for long-term ventilated patients who have severe bronchopulmonary dysplasia.[14] RPPRODs are of clinical usefulness because they are very conservative; the predictive equations developed from these data are very sensitive and accurate in identifying patients who will survive, thus avoiding accidental inclusion of such patients in experimental protocols that are invasive or of unknown or greater risk than that to which the patient would be exposed on mechanical ventilation. Weaknesses of this predictor are its sensitivity to preexisting diseases (such as the upper respiratory tract infection of the misclassified nonsurvivor in this study) that may influence outcome, and to different styles of clinical management, such as the use of sedation, muscle relaxants, and timing of tracheostomy. These weaknesses do not reduce the applicability of this type of analysis; rather, they suggest that optimal results may be obtained by developing these predictors locally. Estimation of this parameter by discriminant function analysis in other disease processes may prove useful in predicting outcome and in identifying patients at risk for complications of ventilator therapy.

REFERENCES

1. Rue LW III, Cioffi WG Jr, Mason AD, et al: Improved survival of burned patients with inhalation injury. Arch Surg 128:772-780, 1993
2. Shirani KZ, Pruitt BA Jr, Mason AD Jr: The influence of inhalation injury and pneumonia on burn mortality. Ann Surg 205:82-87, 1987
3. Pruitt BA Jr: The diagnosis and treatment of infection in the burn patient. Burns 11:79-91, 1984
4. Cioffi WG, Graves TA, McManus WF, et al: High frequency percussive ventilation in patients with inhalation injury. J Trauma 29:350-354, 1989
5. Cioffi WG Jr, Rue LW III, Graves TA, et al: Prophylactic use of high-frequency ventilation in patients with inhalation injury. Ann Surg 213:575-582, 1991
6. Tsuno K, Prato P, Kolobow T: Acute lung injury from mechanical ventilation at moderately high airway pressures. J Appl Physiol 69:956-961, 1990
7. Mammel MC, Boros SJ: Airway damage and mechanical ventilation: A review and commentary. Pediatr Pulmonol 3:443-447, 1987
8. Shirani KZ, Pruitt BA Jr, Mason AD Jr: The influence of inhalation injury and pneumonia on burn mortality. Ann Surg 205:82-87, 1987
9. Hubbard GB, Langlinais PC, Shimazu T, et al: The morphology of smoke inhalation in sheep. J Trauma 31:1477-1486, 1991
10. Arnold JH, Truog RD, Thompson JE, et al: High-frequency oscillatory ventilation in pediatric respiratory failure. Crit Care Med 21:272-278, 1993
11. McCulloch PR, Forkert PG, Froese AB: Lung volume maintenance prevents lung injury during high-frequency oscillatory ventilation in surfactant-deficient rabbits. Am Rev Respir Dis 137:1185-1192, 1988
12. Meredith KS, deLemos RA, Coalson JJ, et al: Role of lung injury in the pathogenesis of hyaline membrane disease in premature baboons. J Appl Physiol 66:2150-2158, 1989
13. Payne NR, Kriesmer P, Mammel M, et al: Comparison of six ECMO selection criteria and analysis of factors influencing their accuracy. Pediatr Pulmonol 11:223-232, 1991
14. Gray PH, Grice JF, Lee MS, et al: Prediction of outcome of preterm infants with severe bronchopulmonary dysplasia. J Paediatr Child Health 29:107-112, 1993